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Validation of a High-Specificity Blood Autoantibody Test to Detect Lung Cancer in Pulmonary Nodules

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Abstract

BACKGROUND: Pulmonary nodules (PNs) are frequently detected by chest CT scan, which is increasingly used in clinical practice. Accurately identifying malignant nodules can pose

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a diagnostic challenge; therefore, a high-specificity biomarker could help clinicians identify malignant nodules and ideally lead to the earlier diagnosis of lung cancer.

RESEARCH QUESTION: What are the performance characteristics of a blood-based biomarker for identifying malignancy in patients with a CT-detected PN?

STUDY DESIGN AND METHODS: Banked plasma samples from 2 independent prospective observational cohorts of patients presenting with benign or malignant PNs 8 to 30 mm in size were tested using a 7-autoantibody panel. Sensitivity, specificity, and positive predictive value of the autoantibody test (AAT) to identify cancer were calculated for the individual and combined cohorts.

RESULTS: Overall, 447 patients (263 and 184 from each cohort) were included in the analysis with a prevalence of malignancy of 55%. The performance of the AAT between the 2 cohorts was similar. The AAT demonstrated a specificity of 90% (95% CI, 85%-93%), a positive predictive value of 66% (95% CI, 52%-77%), sensitivity of 16% (95% CI, 12%-22%), and false-positive rate of 10% in the combined cohort. Using a pretest probability of cancer cutoff of 20% improved the positive predictive value to 76% (95% CI, 61%-88%) and resulted in a 52% decrease in the number of false-positive test results. In the subset of patients who had 18F-fluorodeoxyglucose PET imaging performed for clinical purposes (n = 222), specificity of the AAT was higher (93% vs 58%, $P < .001$), but the sensitivity was lower than 18F-fluorodeoxyglucose PET scan (17% vs 75%, $P < .001$).

INTERPRETATION: This study validates the specificity of a blood-based autoantibody biomarker for identifying malignancy in patients with indeterminate PNs. This rule-in biomarker may help to expedite workup of malignant nodules.

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Keywords

autoantibody; blood-based biomarker; lung cancer; pulmonary nodule; risk reclassification

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The broad use of chest CT scan in the United States has led to the detection of an estimated 1.6 million pulmonary nodules (PNs) annually,[1] which is likely to increase with a rise in lung cancer screening uptake. The prevalence of malignancy in PNs can vary considerably based on practice setting, from approximately 1% in a lung cancer screening setting,[2] to 25% in patients referred to a pulmonologist, and > 75% for patients referred to a thoracic surgeon.[3–6] Due to this variability, accurately identifying malignant nodules poses a diagnostic challenge for clinicians. Guidelines recommend estimating the pretest probability of cancer (pCA) using validated clinical risk prediction models, with low-risk nodules being managed with surveillance and high-risk nodules directed toward biopsy or surgical resection.[7] Most of those encountered in clinical practice are intermediate risk nodules (pCA, 5%-65%), which require further investigation with functional imaging using 18F-fluorodeoxyglucose PET (FDG-PET) or biopsy.[4,7,8] Lack of adherence to guideline-directed management and imprecise methods to quantify cancer risk can result in patients with benign disease undergoing invasive procedures or malignant nodules being inappropriately routed to surveillance, leading to delays in appropriate treatment.[4,8,9]

Interest in noninvasive biomarkers to distinguish benign from malignant PNs has increased over the past decade. Biomarkers can be tuned to increase sensitivity or specificity depending on their intended clinical use.[10,11] A primary goal of a biomarker in this setting is to reclassify intermediate-risk nodules into either a low-risk or high-risk category that can be managed accordingly. For example, a biomarker that is intended to rule out malignancy would ideally have a low false-negative rate, thus optimizing sensitivity and negative predictive value. In contrast, a biomarker intended to rule in malignancy should minimize the false-positive rate by achieving a high specificity and positive predictive value (PPV). For PNs, a high-specificity biomarker could help clinicians identify malignant nodules, ideally leading to earlier diagnosis and treatment of cancer without substantially increasing the rate of inappropriate procedures for benign disease.

Nodify CDT (Biodesix Inc) is a rule-in, blood-based biomarker intended to identify malignancy for patients with indeterminate PNs. The blood test detects the presence of 7 serum autoantibodies (AAbs) to a panel of lung cancer-associated antigens using an indirect enzyme-linked immunosorbent assay method.[12–14] We undertook this study to validate the performance of the autoantibody test (AAT) to identify malignant nodules in 2 separate cohorts. In addition, we aimed to compare the test characteristics of the AAT and an imaging-based biomarker, FDG-PET scan.

Study Design and Methods

Patient Cohorts

This was a retrospective analysis of 2 independent, prospectively enrolled cohorts of patients presenting with lung nodules. All sites had institutional review board approval, and informed written consent was obtained from all eligible participants.

The Pulmonary Nodule Plasma Proteomic Classifier (PANOPTIC) was a multicenter, prospective, observational trial (NCT01752114) detailed previously.[15] Briefly, patients were enrolled across 33 sites between November 2012 and December 2015. Patients included were aged ≥ 40 years with PNs 8 to 30 mm in diameter who presented within 60 days of baseline CT scan.

Exclusion criteria included any of the following: prior attempt at biopsy of nodule in question, previous CT scan outside the 60-day window or FDG-PET scan identifying the nodule in question, current or previous diagnosis of cancer within 2 years of nodule detection, or having received any blood products within 30 days of study enrollment. Patients with subsolid nodules were included.

The Fred Hutchinson Cancer Center (FHCC) cohort prospectively enrolled patients who presented to the center for evaluation of a lung nodule, including solid and subsolid nodules, between the years of 2010 and 2020 at the FHCC outpatient clinic or the University of Washington thoracic surgery clinic. For this study, patients were identified with lung cancer or a definitive benign diagnosis based on clinical or imaging follow-up. To match intended use criteria of the biomarker with PANOPTIC, patients were excluded for the following: age

< 40 years, nodule < 8 or > 30 mm in size, prior history of cancer within 5 years, or evidence of mediastinal lymphadenopathy at cancer diagnosis.

For both cohorts, banked plasma samples were analyzed for the AAT and correlated with clinical outcomes. Investigators performing AAT analysis were masked to patient outcomes. For the PANOPTIC cohort, nodules were classified as benign based on either confirmed benign pathologic diagnosis (eg, granuloma, hamartoma, infection, fibrosis) or CT stability or resolution at 12 months; however, most (94%) had 2 years of stability.[16] For the FHCC cohort, nodules were classified as benign based on either confirmed benign pathologic diagnosis (eg, granuloma, hamartoma, infection, fibrosis), evidence of infection or CT stability, or resolution on ≥ 1 year of follow-up imaging, with most stable nodules (74%) having 2 years of follow-up. Malignant diagnoses were established by histopathology at both sites. Patient demographics and nodule characteristics were collected at baseline. Nodule characteristics (spiculation, size, and edge characteristics) were extracted from radiologist reports at each site. For patients with complete clinical data, clinical and nodule characteristics were compared between those included and those excluded.

Aab Assay

The blood test detects the presence of AAbs to a panel of 7 lung cancer-associated antigens (p53, NY-ESO-1, MAGE A1, GBU4–5, CAGE, HuD, and SOX2) using indirect enzyme-linked immunosorbent assay. Technical and clinical validation of the assay have been previously reported.[13,14,17,18] Test results are considered positive if the concentration of at least 1 AAb is higher than a predetermined cutoff level, with positive results further stratified as moderate level or high level detected based on previously reported thresholds.[17,19] Moderate-level positive test includes all positive test results based on initial assay cutoffs,[17] whereas high-level positive test includes only tests with AAb levels greater than reoptimized assay cutoffs with fixed specificity of 98% in the optimization cohort.[19] A negative test result, also indicated as no significant level of Aabs detected, indicates that none of the 7 AAb concentrations are elevated above their predetermined cutoffs.

For subgroup analyses, we assessed the performance of the AAT in the combined cohorts and compared with FDG-PET scan in a subset of patients who had undergone both tests. FDG-PET scans were considered positive if by report the maximum standardized uptake value was ≥ 2.5, described as fluorodeoxyglucose avid, or hypermetabolic, whereas FDG-PET scans were considered negative if the maximum standardized uptake value was < 2.5 or labeled as mild, minimal, negative, not hypermetabolic, not PET avid, or with no uptake. In addition, we assessed the performance of the biomarker after excluding both ground-glass and part-solid nodules.

Statistical Analysis

Statistical analyses were carried out using R (version 4.0.4 or later [R Foundation for Statistical Computing]). Continuous variables were compared between groups using Welch *t* test, and categorical variables were compared using Fisher exact test. The performance of the biomarker test was assessed using standard metrics including sensitivity, specificity, false-positive rate, and PPV. The 95% CIs for all performance metrics were generated

using the exact binomial method. For unpaired cohorts (ie, FHCC vs PANOPTIC), test performance metrics were compared using Fisher exact test, whereas comparison of performance metrics of paired tests in a single cohort (ie, FDG-PET scan vs AAT test) were compared using the McNemar test and the generalized score statistic.[20]

Posttest probability was calculated by first determining a patient's pCA using the Mayo model[21] and adjusting the probability using previously reported likelihood ratios for the 2 AAT cutoffs defined as moderate level or high level.[17,19] Risk reclassification was evaluated by comparing pCA and posttest probability of cancer against the American College of Chest Physicians (CHEST) guideline risk thresholds of 5% and 65%.[7] Sensitivity analyses were carried out by sequentially calculating diagnostic performance at 10% increments ranging from pCA 0% to 70%. For patients presenting with solid nodules with eventual malignant diagnosis, time to diagnosis was calculated based on time of initial suspicious CT scan to final diagnosis of cancer, either by biopsy or surgical pathology.

Results

This study evaluated a cohort consisting of 447 patients (PANOPTIC: n = 263, FHCC: n = 184) (Fig 1). Differences between those included and excluded are presented in e-Table 1. Overall, the 2 cohorts were similar in terms of prevalence of malignancy, smoking history, gender, nodule size, and location (Table 1). The PANOPTIC cohort had a higher rate of spiculated nodules (40% vs 12%, $P < .001$) and higher average pCA compared with the FHCC cohort (0.40 vs 0.30, $P < .001$). The FHCC cohort included 35 nodules (19%) detected by lung cancer screening, whereas the PANOPTIC cohort consisted of incidentally detected nodules only. The prevalence of malignancy was 55%, and the AAT was positive in 14% of patients. The median time to diagnosis of lung cancer for patients who had a solid PN was 1.86 months (interquartile range, 1.01–7.15) from nodule detection, and 67% were diagnosed within a 3-month window (e-Fig 1).

The AAT showed similar performance across both cohorts for moderate-level and high-level test thresholds (Table 2); therefore, the remainder of the analysis was performed using the combined cohort. A positive AAT demonstrated a specificity of 90% (95% CI, 85%-93%), sensitivity of 16% (95% CI, 12%-22%), and a PPV of 66% (95% CI, 52%-77%) (e-Table 2). Lung cancer was diagnosed in 40 of 61 patients with a positive AAT, yielding a false-positive rate of 10% (21 of 208). A subgroup analysis demonstrated no change in results when patients with ground-glass and part-solid nodules were excluded (e-Table 3).

When the analysis was limited to patients with a higher pretest pCA, the AAT showed increased sensitivity, specificity, and PPV, with a steady increase in performance as the pCA cutoff increased (Fig 2). When comparing all patients regardless of pCA with only those with pCA > 70%, sensitivity ranged from 16% to 22%, specificity from 90% to 100%, and PPV from 66% to 100%. We noted an inflection point in specificity at a pCA threshold of 0.20 to 0.30. At a pCA of 0.20, the AAT had a sensitivity of 16% (95% CI, 11%-22%), specificity of 90% (95% CI, 82%-95%), and PPV of 76% (95% CI, 61%-88%) and was positive in 14.3% of patients (42 of 294) (Table 3). At this threshold, malignancy was diagnosed in 32 of 42 patients with a positive test, decreasing the number of false-positive

results by 52% (10 vs 21) compared with the overall cohort. Moving to a cutoff threshold of 0.1, the specificity was similar (89%); however, there was an increase in the absolute number of false-positive tests (16 vs 10) and a lower PPV (0.71 vs 0.76).

For patients with a positive AAT, 16 malignant nodules with intermediate pCA were appropriately reclassified as high risk using the AAT, compared with 10 benign nodules inappropriately reclassified (Fig 3). Importantly, no nodules with a low pCA (< 5%) were misclassified as positive by the AAT. At an inclusion threshold of 0.2 pCA, 13 malignant nodules and 8 benign nodules were reclassified as high risk (e-Fig 2).

The accuracy of the AAT was then compared with FDG-PET using a subset of patients who had been tested with both (n = 222; PANOPTIC: n = 141, FHCC: n = 81). The prevalence of malignancy in this subset was higher than the overall cohort (73% vs 55%; $P < .001$) (e-Table 4). The AAT was positive in 14% of patients (31 of 222), and FDG-PET was positive in 66% of patients (147 of 222). Although sensitivity of the AAT was lower than FDG-PET (17% vs 75%; $P < .001$), the specificity of the AAT was higher (93% vs 58%; $P < .001$) (Table 4). These results did not change when patients with ground-glass and part-solid nodules were excluded (e-Table 5). In the FDG-PET tested cohort, 7% of patients (4 of 60) with benign disease had a false-positive AAT, compared with 42% (25 of 60) with false-positive results by FDG-PET testing.

Discussion

This study validates a previous analysis of the AAT in patients with an indeterminate PN which discovered a nearly 3-fold increase in the risk of malignancy for those with a positive test result.[18] It also represents the first external clinical validation to our knowledge of the AAT in a population of patients presenting with indeterminate PNs. During this validation, we identified similar test performances between 2 distinct cohorts with an improved specificity and PPV for identifying cancer when compared with the initial development and optimization cohorts.[18,19] In subgroup analyses, we found that the AAT performed better in patients with a pCA of ≥ 20% and had a significantly improved specificity when compared with FDG-PET. Furthermore, the performance of the test was similar when patients with ground-glass and part-solid nodules were excluded.

Other Aab assays have been developed for use in the evaluation of indeterminate PNs, but they remain in earlier phases of discovery. For example, Lastwika et al[22] have developed a 4-Aab panel with a sensitivity of 91% and specificity of 57% to diagnose indeterminate PNs 8 to 20 mm in size. Wang et al[23] have developed a 5-Aab assay with a specificity of 88% and sensitivity of 30% to distinguish malignant from benign nodules. Another 7-Aab panel with several overlapping tumor-associated AAb to the blood biomarker tested in this study demonstrated a sensitivity of 68%, specificity of 74%, and PPV of 56% for distinguishing benign from early stage malignant PNs.[24] The performance characteristics of the AAT evaluated here in 2 independent, prospectively collected nodule cohorts demonstrated higher specificity but was limited in sensitivity. Another biomarker test, a genomic classifier from nasal squamous epithelium, has been validated with a sensitivity of 58% and specificity of 90% for the high-risk classifier. However, this test has only been validated in people

with active or previous tobacco use.[25] In contrast, the AAT described here could be used more broadly in all patients presenting with indeterminate PNs regardless of smoking status. Determining the optimum pCA threshold for use of the AAT is challenging. When the test was applied to all comers regardless of pCA, the PPV was 66%, yielding 21 false-positive results, which may be higher than would be acceptable for clinicians using the test. Although increasing the pCA cutoff will lead to a higher PPV and fewer false positives, this comes at the cost of fewer malignant nodules identified. Prior work on the AAT has demonstrated that a pCA cutoff of 0.30 significantly reduced the number of false-positive tests while still detecting nearly one-half the number of malignant nodules.[18] In this study, we performed a sensitivity analysis to probe this cutoff and identified a threshold that would balance minimizing false-positive results while still detecting malignant nodules. This analysis validated the previously reported performance using a pCA > 0.3 threshold that was sustained at a lower pCA threshold of 0.2. Furthermore, using the AAT at a pCA threshold of 0.2 decreased false-positive results by one-half compared with the overall cohort while detecting a greater number of malignant nodules than the 0.3 cutoff. Decreasing the cutoff further (ie, to a pCA of 0.1) only increased the absolute number of false-positive results and decreased the PPV. This analysis highlights that a one-size-fits-all approach to evaluate intermediate risk nodules as currently defined by guidelines (5%-65%)[7] may not be appropriate and that a more granular risk stratification within this group may be warranted. Although further work is needed to validate these results, this analysis suggests that the AAT may be most useful when applied to patients with an intermediate risk of malignancy > 20% to determine those most in need of expedited biopsy or surgery.

The specificity of FDG-PET was low in this study, with a false-positive rate of 42%. Although earlier studies of FDG-PET reported high sensitivity and specificity (97% and 78%, respectively) for the diagnosis of PNs and mass lesions,[26] a more recent meta-analysis of FDG-PET performance has shown significant heterogeneity across studies with a pooled sensitivity of 89% (95% CI, 86%-91%) and specificity of 75% (95% CI, 71%-79%).[27] Furthermore, the specificity of FDG-PET is decreased in areas with endemic fungal infections.[27,28] Although fewer malignant nodules were identified with use of the AAT, the false-positive rate was significantly lower at 7% vs 42% in the subgroup of patients that had both tests performed. The use of FDG-PET and the AAT may be complementary in the approach to nodule evaluation based on different test performance characteristics, but further investigation is needed.

Delays in the diagnosis and treatment of lung cancer are common and can lead to worse outcomes.[29,30] We found that one-third of the patients with cancer in this cohort had a workup lasting > 3 months, which is a commonly used surveillance imaging time for concerning lesions. Among patients with early stage lung cancer undergoing surgical resection, 1 study found that patients who waited > 12 weeks to undergo surgery after nodule identification had an increased risk of recurrence and worse survival compared with patients receiving definitive treatment within 12 weeks of nodule identification.[31] Ideally, the AAT should be used to identify patients with higher risk of malignancy who require expedited workup, which may include nonsurgical biopsy or surgical resection depending on physician recommendation and patient preferences. A clinical utility study is needed to

fully evaluate the benefits of the AAT on timelines of care and the harms associated with false-positive results.

This study demonstrates that with its high specificity, the 7-panel AAT may be useful to rule-in lung cancer in patients with an intermediate risk of malignancy. A high-sensitivity blood test may provide complementary diagnostic information to rule-out patients with benign disease.[15,32] Assuming minimal overlap between the 2 tests, a combination of 2 biomarkers could potentially correctly reclassify up to 50% of indeterminate PNs.[15] Future work should assess the use of both sensitive and specific biomarkers in combination for lung nodule evaluation.

Our study has several limitations related to the retrospective nature of the study. First, there were a number of patients from the PANOPTIC cohort who did not have sufficient banked sample available for AAT analysis that could result in selection bias. However, for those with complete clinical data in the PANOPTIC cohort (n = 392), aside from history of cancer, demographic and nodule characteristics were similar between included and excluded patients. Second, in the FHCC biorepository only patients with known specific benign disease or CT stability at ≥ 1 year were included in the controls, and patients with known malignant diagnoses other than non-small cell lung cancer were excluded, which may not reflect the general population of patients presenting with indeterminate nodules and may have introduced selection bias. Similarly, only a subgroup of patients had FDG-PET data available for analysis because the decision to order FDG-PET was at the discretion of the treating physician. In addition, there may have been differences in nodule management between the real-world FHCC cohort and the clinical trial cohort from PANOPTIC, which may have impacted factors (eg, time to diagnosis). There was a large amount of missing data regarding nodule density in the PANOPTIC cohort, which precluded performing the analysis only in patients with solid nodules. Ideally, test performance should be further validated in a cohort of exclusively solid nodules and examined in larger groups of subsolid nodules. Finally, we used previously reported likelihood ratios for the risk reclassification analysis that correspond with the use of the test because it is currently clinically available, but further refinement of these likelihood ratios may lead to improved reclassification in the future.

Interpretation

Accurately identifying malignant PNs without the use of invasive procedures remains a clinical challenge. This study validated the specificity of a blood-based Aab biomarker to identify malignancy in patients with indeterminate nodules. The low false-positive rate of the AAT in comparison with FDG-PET may make this rulein test a useful adjunct in clinical practice. Use in combination with sensitive rule-out biomarkers may lead to improvement in the management of intermediate risk nodules, to ensure benign nodules do not undergo invasive testing and malignant nodules are rapidly identified and resected. Further study is warranted to assess the test's clinical utility alongside FDG-PET imaging, and its effect on the timeliness of care and appropriate utilization of procedures in patients presenting with indeterminate PNs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

Aab	autoantibody
AAT	autoantibody test
FDG-PET	18F-fluorodeoxyglucose PET
FHCC	Fred Hutchinson Cancer Center
PANOPTIC	Pulmonary Nodule Plasma Proteomic Classifier
pCA	pretest probability of cancer
PN	pulmonary nodule
PPV	positive predictive value

References

1. Gould MK, Tang T, Liu IL, et al. Recent trends in the identification of incidental pulmonary nodules. Am J Respir Crit Care Med, 192. 2015;(10),:1208–1214. [PubMed: 26214244]
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409. [PubMed: 21714641]
3. Vachani A, Zheng C, Amy Liu IL, Huang BZ, Osuji TA, Gould MK. The probability of lung cancer in patients with incidentally detected pulmonary nodules: clinical characteristics and accuracy of prediction models. Chest. 2022;161(2):562–571. [PubMed: 34364866]
4. Tanner NT, Aggarwal J, Gould MK, et al. Management of pulmonary nodules by community pulmonologists: a multicenter observational study. Chest. 2015;148(6):1405–1414. [PubMed: 26087071]
5. Maiga AW, Deppen SA, Mercaldo SF, et al. Assessment of fluorodeoxyglucose F18-labeled positron emission tomography for diagnosis of high-risk lung nodules. JAMA Surg. 2018;153(4):329–334. [PubMed: 29117314]

6. Godfrey CM, Shipe ME, Welty VF, et al. The thoracic research evaluation and treatment 2.0 model: a lung cancer prediction model for indeterminate nodules referred for specialist evaluation. Chest. 2023;164(5):1305–1314. [PubMed: 37421973]
7. Gould MK, Donnington J, Lynch WR, Mazzone PJ, Midthun DR, Naidich DP, Wiener RS. Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 suppl):e93S–e120S. [PubMed: 23649456]
8. Tanner NT, Porter A, Gould MK, Li XJ, Vachani A, Silvestri GA. Physician assessment of pretest probability of malignancy and adherence with guidelines for pulmonary nodule evaluation. Chest. 2017;152(2):263–270. [PubMed: 28115167]
9. Wiener RS, Gould MK, Slatore CG, Fincke BG, Schwartz LM, Woloshin S. Resource use and guideline concordance in evaluation of pulmonary nodules for cancer: too much and too little care. JAMA Intern Med. 2014;174(6):871–880. [PubMed: 24710850]
10. Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating molecular biomarkers for the early detection of lung cancer: When is a biomarker ready for clinical use? An Official American Thoracic Society Policy Statement. Am J Respir Crit Care Med. 2017;196(7):e15–e29. [PubMed: 28960111]
11. Chabon JJ, Hamilton EG, Kurtz DM, et al. Integrating genomic features for non-invasive early lung cancer detection. Nature. 2020;580(7802):245–251. [PubMed: 32269342]
12. Chapman CJ, Murray A, McElveen JE, et al. Autoantibodies in lung cancer: possibilities for early detection and subsequent cure. Thorax. 2008;63(3):228–233. [PubMed: 17932110]
13. Murray A, Chapman CJ, Healey G, et al. Technical validation of an autoantibody test for lung cancer. Ann Oncol. 2010;21(8):1687–1693. [PubMed: 20124350]
14. Boyle P, Chapman CJ, Holdenrieder S, et al. Clinical validation of an autoantibody test for lung cancer. Ann Oncol. 2011;22(2):383–389. [PubMed: 20675559]
15. Silvestri GA, Tanner NT, Kearney P, et al. Assessment of plasma proteomics biomarker's ability to distinguish benign from malignant lung nodules: results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) trial. Chest. 2018;154(3):491–500. [PubMed: 29496499]
16. Tanner NT, Springmeyer SC, Porter A, Jett JR, Mazzone P, Vachani A, Silvestri GA. Assessment of integrated classifier's ability to distinguish benign from malignant lung nodules: extended analyses and 2-year follow-up results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) trial. Chest. 2021;159(3):1283–1287. [PubMed: 33171158]
17. Chapman CJ, Healey GF, Murray A, et al. EarlyCDT(R)-Lung test: improved clinical utility through additional autoantibody assays. Tumour Biol. 2012;33(5):1319–1326. [PubMed: 22492236]
18. Massion PP, Healey GF, Peek LJ,, et al. Autoantibody signature enhances the positive predictive power of computed tomography and nodule-based risk models for detection of lung cancer. J Thorac Oncol. 2017;12(3):578–584. [PubMed: 27615397]
19. Healey G, Macdonald I, Reynolds C, Allen J, Murray A. Tumor-associated autoantibodies: re-optimization of EarlyCDT-lung diagnostic performance and its application to indeterminate pulmonary nodules. Journal of Cancer Therapy. 2017;8:506–517.
20. Leisenring W, Alonzo A, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. Biometrics. 2000;56(2):345–351. [PubMed: 10877288]
21. Swensen SJ, SIlverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med. 1997;157(8):849–855. [PubMed: 9129544]
22. Lastwika KJ, Kargl J, Zhang Y, et al. Tumor-derived autoantibodies identify malignant pulmonary nodules. Am J Respir Crit Care Med. 2019;199(10):1257–1266. [PubMed: 30422669]
23. Wang J, Shivakumar S, Barker K, et al. Comparative study of autoantibody responses between lung adenocarcinoma and benign pulmonary nodules. J Thorac Oncol. 2016;11(3):334–345. [PubMed: 26896032]
24. Ling Z, Chen J, Wen Z, Wei X, Su R, Tang Z, Hu Z. The value of a seven-autoantibody panel combined with the Mayo model in the differential diagnosis of pulmonary nodules. Dis Markers. 2021;2021:6677823. [PubMed: 33688380]

25. Lamb CR, Rieger-Christ KM, Reddy C, et al. A nasal swab classifier to evaluate the probability of lung cancer in patients with pulmonary nodules. Chest. 2024;165(4):1009–1019. [PubMed: 38030063]

26. Gould MK Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA. 2001;285(7):914–924. [PubMed: 11180735]

27. Deppen SA, Blume JD, Kensinger CD, et al. Accuracy of FDG-PET to diagnose lung cancer in areas with infectious lung disease: a meta-analysis. JAMA. 2014;312(12):1227–1236. [PubMed: 25247519]

28. Deppen S, Putnam JB Jr., Andrade G, et al. Accuracy of FDG-PET to diagnose lung cancer in a region of endemic granulomatous disease. Ann Thorac Surg. 2011;92(2):428–432. [PubMed: 21592456]

29. Jacobsen MM, Silverstein SC, Quinn M, Water, et al. Timeliness of access to lung cancer diagnosis and treatment: a scoping literature review. Lung Cancer. 2017;112:156–164. [PubMed: 29191588]

30. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087. [PubMed: 33148535]

31. Heiden BT, Eaton DB Jr. Engelhardt KE, et al. Analysis of delayed surgical treatment and oncologic outcomes in clinical stage I non-small cell lung cancer. JAMA Netw Open. 2021;4(5):e2111613. [PubMed: 34042991]

32. Pritchett MA, Sigal B, Bowling MR, Kurman JS, Pitcher T, Springmeyer SC, Investigators OS. Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: results from the ORACLE study. PLoS One. 2023;18(7):e0287409. [PubMed: 37432960]

Take-Home Points

Study question:

Can a blood-based biomarker of autoantibodies associated with lung cancer development identify pulmonary nodules that are lung cancer?

Results:

A blood-based autoantibody test performed similar in 2 separate cohorts with an overall specificity of 90%, a positive predictive value of 66%, and a false-positive rate of 10%.

Interpretation:

Our findings show that the autoantibody test has reproducible test performance characteristics in separate cohorts of patients with pulmonary nodules that may assist clinicians with identifying lung cancer in higher-risk individuals.

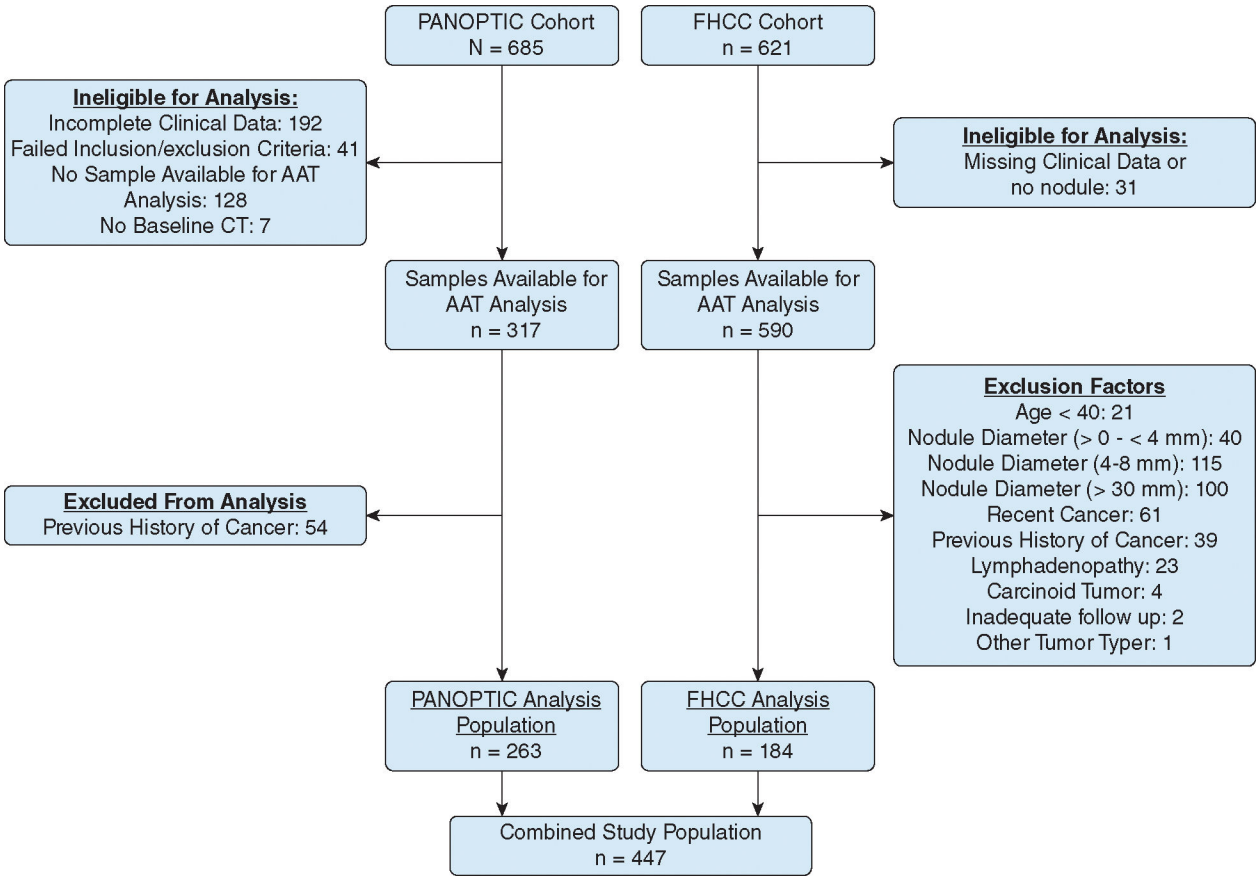

Figure 1 –.

Flowchart of patients included in autoantibody test analysis from 2 cohorts. Of the 685 patients enrolled in the PANOPTIC trial, 368 were ineligible for analysis leaving 263 for analysis. From 621 patients in the FHCC cohort, 437 were ineligible for analysis leaving 184 for analysis. The combined cohort consisted of 447 patients. AAT = autoantibody test; FHCC = Fred Hutchinson Cancer Center; PANOPTIC = Pulmonary Nodule Plasma Proteomic Classifier.

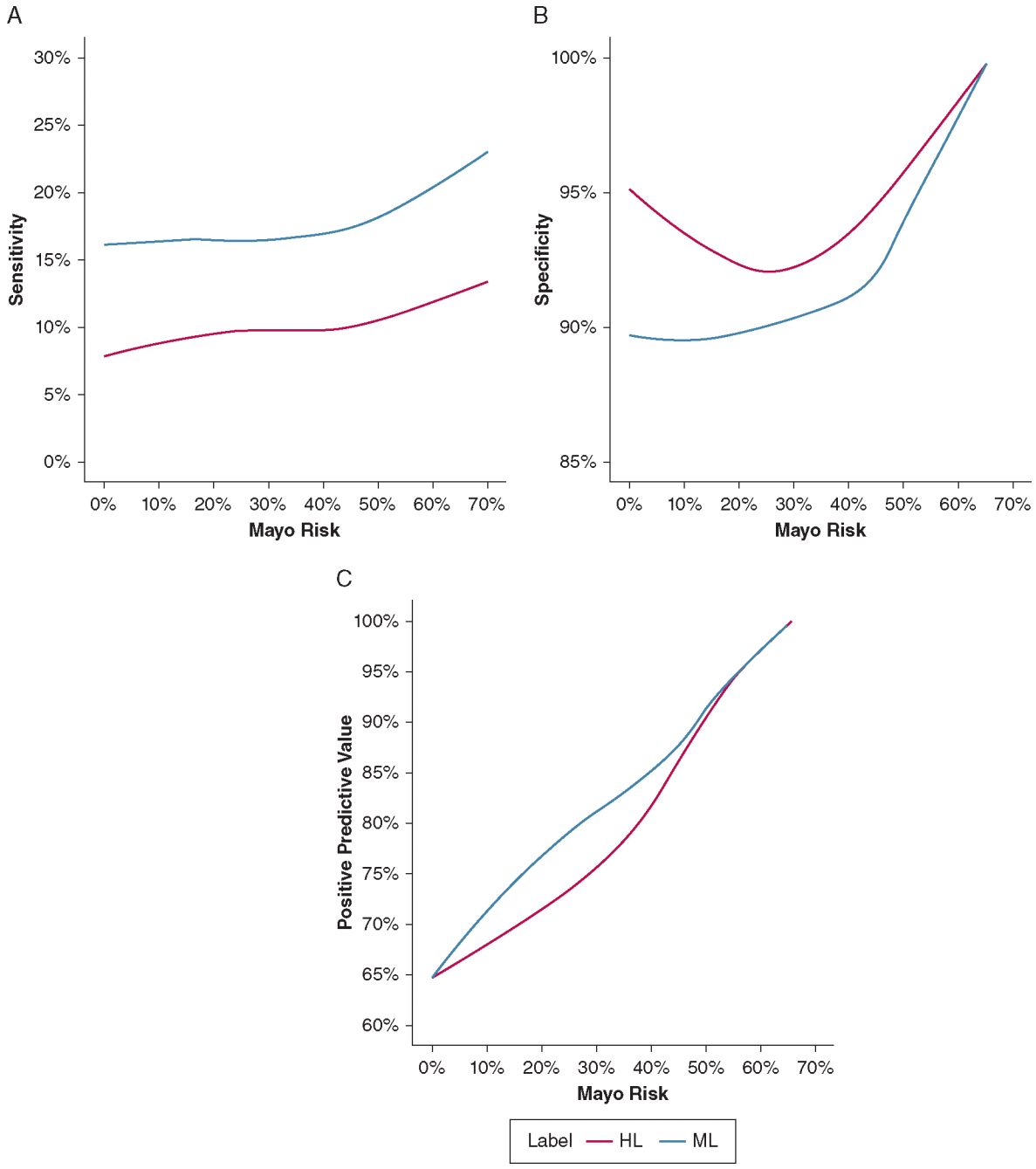

Figure 2 –.

A-C, Performance of autoantibody test by pretest probability of cancer (pCA). Shown are (A) sensitivity, (B) specificity, and (C) positive predictive value across a range of pCA cutoffs from 0% to 70%. An ML positive test is indicated by the red line, and an HL positive test is indicated by the blue line. Lines are smoothed for clarity. HL = high level; ML = moderate level.

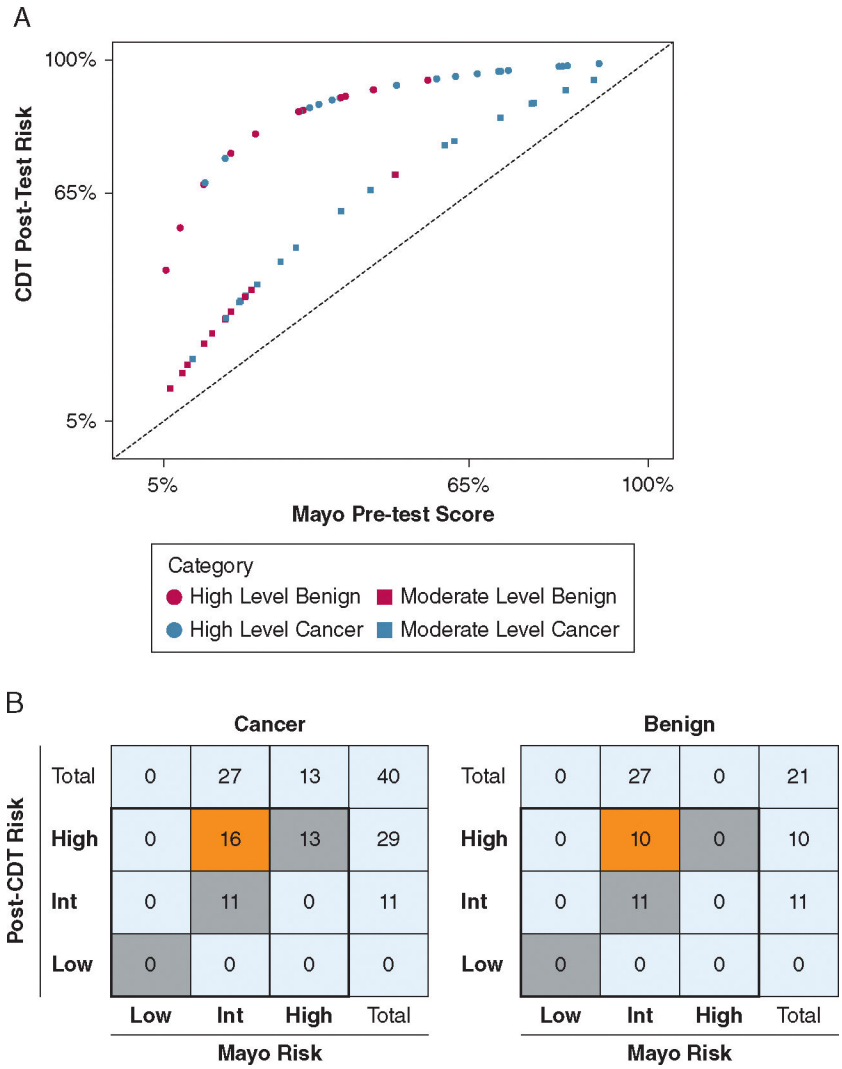

Figure 3 –.

A, B, Risk reclassification for patients with a positive autoantibody test. A, Pretest probability of cancer calculated by the Mayo model is plotted on the x-axis with posttest risk after applying the autoantibody test plotted on the y-axis. A moderate-level positive threshold is represented by squares and a high-level positive threshold by circles. Benign nodules are designated in blue and malignant nodules in red. Cutoffs for low risk (< 5%) and high risk (> 65%) are marked to show change in risk category after testing. The dotted diagonal line represents no change in posttest risk. B, Reclassification tables showing the number of nodules in each pretest and posttest risk category (low < 5%, intermediate [Int] 5%-65%, high > 65%). The orange shaded squares denote nodules that have been reclassified into a higher risk category after testing. The gray shaded squares denote nodules that have not changed risk category following testing.

TABLE 1]

Demographics by Lung Nodule Cohort

Characteristic	Overall (N = 447)	FHCC (n = 184)	PANOPTIC (n = 263)	*P* Value[a]
Diagnosis				.70
Benign	202 (45)	81 (44)	121 (46)	
Imaging based	130 (64)	47 (58)	83 (69)	
Specific diagnosis[b]	72 (36)	34 (42)	38 (31)	
Lung Cancer	245 (55)	103 (56)	142 (54)	
Age, y	66 [10]	65 [10]	66 [10]	.40
Gender				.60
Woman	223 (50)	95 (52)	128 (49)	
Man	224 (50)	89 (48)	135 (51)	
Smoking history				.11
Active/previous	361 (81)	142 (77)	219 (83)	
Never smoked	86 (19)	42 (23)	44 (17)	
Nodule diameter, mm	16.7 [6.1]	16 [6]	17.1 [6.2]	.05
Nodule size category, mm				.023
8–10	88 (20)	46 (25)	42 (16)	
11–20	244 (55)	100 (54)	144 (55)	
21–30	115 (26)	38 (21)	77 (29)	
Spiculation	128 (29)	22 (12)	106 (40)	< .001
Lobe location				.80
Other	186 (42)	78 (42)	108 (41)	
Upper	261 (58)	106 (58)	155 (59)	
Mayo pretest score	0.36 [0.24]	0.30 [0.22]	0.40 [0.24]	< .001
AAT result				.01
Moderate level	30 (6.7)	19 (10)	11 (4.2)	
High level	31 (6.9)	8 (4.3)	23 (8.7)	
NSLAD	386 (86)	157 (85)	229 (87)	

Categorical variables are shown as No. (%) and continuous variables are shown as mean [SD]. AAT = autoantibody test; FHCC = Fred Hutchinson Cancer Center; NSLAD = no significant level of autoantibodies detected; PANOPTIC = Pulmonary Nodule Plasma Proteomic Classifier.

[a] Fisher exact test and Welch *t* test.

[b] Including granuloma, infection, hamartoma, sarcoid, and fibrosis.

TABLE 2]

Autoantibody Test Performance by Lung Nodule Cohort

Cohort	Any Positive Test				High-Level Positive Test			
	Combined	FHCC (n = 184)	PANOPTIC (n = 263)	*P* Value[a]	Combined	FHCC (n = 184)	PANOPTIC (n = 263)	*P* Value[a]
Disease prevalence, %	55 (50–59)	56 (48–63)	54 (48–60)	.70	55 (50–59)	56 (48–63)	54 (48–60)	.70
Sensitivity, %	16 (12–22)	15 (8–23)	18 (12–25)	.60	8 (5–12)	4 (1–10)	11 (7–18)	.06
Specificity, %	90 (85–93)	85 (77–92)	93 (86–97)	.10	95 (90–97)	95 (88–99)	94 (88–98)	> .99
FPR, %	10 (6–15)	15 (8–23)	7 (3–14)	.10	5 (3–9)	5 (1–12)	6 (2–12)	> .99
PPV, %	66 (55–77)	56 (35–75)	74 (56–87)	.20	65 (45–81)	50 (16–84)	70 (47–87)	.40

Values are shown as percentage (95% CI) using an exact binomial method or as otherwise indicated. FHCC = Fred Flutchinson Cancer Center; FRP = false-positive rate; PANOPTIC = Pulmonary Nodule Plasma Proteomic Classifier; PPV = positive predictive value.

[a]Fisher exact test.

TABLE 3]

Autoantibody Test Performance Across Increasing Pretest Probability of Cancer

Performance	All pCA	pCA > 10%	pCA > 20%	pCA > 30%	pCA > 45%	pCA > 60%
Disease prevalence, %	55	60	67	71	79	86
Sensitivity, %[a]	16 (12–22)	17 (13–23)	16 (11–22)	17 (12–24)	18 (11–26)	21 (12–32)
Specificity, %	90 (85–95)	89 (84–94)	90 (82–95)	89 (79–96)	91 (71–98)	100 (75–100)
FPR, %	10 (7–15)	10 (6–16)	10 (5–18)	11 (4–21)	9 (12–25)	0
PPV, %	66 (52–77)	71 (58–83)	76 (61–88)	80 (63–92)	88 (68–97)	100 (79–100)
Percent of cohort	100	86 (386/447)	66 (294/447)	52 (231/447)	33 (150/447)	20 (90/447)
% of total cancers	100 (245)	99 (244/245)	80 (196/245)	67 (165/245)	48 (118/245)	31 (77/245)
% positive test	14 (61/447)	14 (56/386)	14 (42/294)	15 (35/231)	16 (24/150)	18 (16/90)

Values are down as percentage (95% CI) unless otherwise indicated. FPR = false-positive rate; pCA = pretest probability of cancer; PPV = positive predictive value.

[a]95% CI using an exact binomial method.

TABLE 4]

Performance of Autoantibody Test and FDG-PET Scan (n = 222)

Performance	AAT Performance	FDG-PET Performance	*P* Value[a]
Disease prevalence, %	73 (67–79)	73 (67–79)	NA
Sensitivity, %	17 (11–23)	75 (68–82)	< .001
Specificity, %	93 (84–98)	58 (44–71)	< .001
FPR, %	7 (2–16)	42 (29–55)	< .001
PPV, %	87 (70–96)	83 (76–89)	.525[b]

Values are shown as percentage (95% CI) using an exact binomial method or as otherwise indicated. AAT = autoantibody test; FDG-PET = 18F-fluorodeoxyglucose PET; FPR = false-positive rate; NA = not applicable; PPV = positive predictive value.

[a]McNemar test.

[b]Generalized score statistic.